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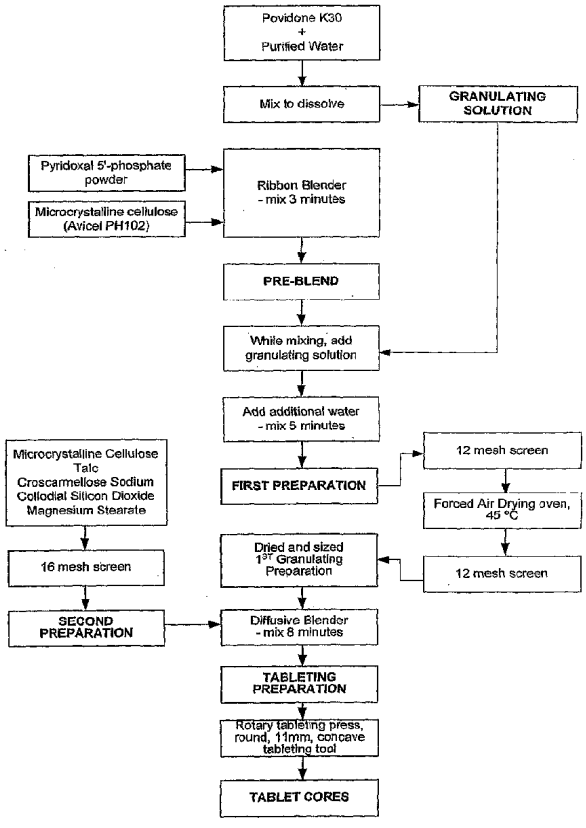
(54) Title: FORMULATIONS OF PYRIDOXAL -5'-PHOSPHATE AND METHODS OF PREPARATION



(57) Abstract: The present invention provides pharmaceutical compositions for oral administration comprising pyridoxal-5'-phosphate wherein the compositions contain an amount of pyridoxal-5-phosphate of at least 50% w/w and methods of preparing the pharmaceutical compositions. The present invention also provides a pre-blend for the manufacture of a pyridoxal 5'-phosphate oral dosage form comprising pyridoxal 5'-phosphate and microcrystalline cellulose, wherein the pre-blend contains an amount pyridoxal-5-phosphate greater than or equal to 80% w/w.

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Title: Formulations of Pyridoxal-5'-phosphate and Methods of Preparation

Field of Invention

[0001] The present invention relates to pharmaceutical formulations of pyridoxal-5'-phosphate and methods of preparing the same.

Background

[0002] Pyridoxal 5'-phosphate is useful for the treatment and prevention of a variety of diseases such as hypertension, cerebrovascular disorders, cardiovascular disorders and diabetes. See for example US patent numbers 6,051,587; 6,417,204; 6,548,519; 6,586,414; 6,605,612; 6,667,315; 6,780,997; 6,677,356; 6,489,348; and 6,043,259. Pyridoxal 5'-phosphate is commercially available in variety of doses. However, currently available supplements generally deliver lower doses of pyridoxal 5'-phosphate which are too low for the treatment of hypertension, cerebrovascular disorders, cardiovascular disorders and diabetes. As such, it is often necessary for the supplement to be administered several times daily in ordered to achieve suitable therapeutic levels.

[0003] The present invention provides novel oral pharmaceutical compositions capable of delivering increased amounts of pyridoxal 5'-phosphate as compared to prior art formulations. The present invention also provides novel pharmaceutical compositions which overcome gastrointestinal side effects associated with the intake of high doses of pyridoxal 5'-phosphate.

Summary of Invention

[0004] In a first aspect, the invention provides a pharmaceutical composition for oral administration comprising: pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof, a disintegrant, a binding agent, a

lubricant, a glidant and an anti-adherent wherein the composition contains an amount of pyridoxal-5'-phosphate of at least 50% w/w.

[0005] In an embodiment of the invention, the pharmaceutical composition further comprises a glidant. The glidant may be colloidal silcon dioxide.

[0006] In an embodiment of the invention, the pharmaceutical composition further comprises an anti-adherent. The anti-adherent may be talc.

[0007] In an embodiment of the invention, the pharmaceutical composition comprises about 66.3% w/w pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof; about 3.0% w/w croscarmellose sodium as the disintegrant; about 4.7% w/w povidone and about 22.2% w/w microcrystalline cellulose as the binding agent; about 0.6% colloidal silicon dioxide as the glidant; about 1.1% w/w magnesium stearate as the lubricant and about 2.3% talc as the anti-adherent.

[0008] In an embodiment of the invention, the pharmaceutical composition is in the form of a tablet comprising: (a) a core, wherein said core comprises the pyridoxal-5'-phosphate or pharmaceutically acceptable salt, the disintegrant, the binding agent, and the lubricant; (b) a sealing coat surrounding the core; and (c) an enteric coat surrounding the sealing coat.

[0009] In an embodiment of the invention, the pharmaceutical composition is in the form of a tablet comprising: (a) a core, wherein said core comprises the pyridoxal-5'-phosphate or pharmaceutically acceptable salt, the disintegrant, the binding agent, the lubricant, the glidant and the anti-adherent; (b) a sealing coat surrounding the core; and (c) an enteric coat surrounding the seaing coat.

[00010] In an embodiment of the invention, the sealing coat is Opadryl-IR-7000 White.

[00011] In an embodiment of the invention, the amount of Opadryl-IR-7000 White is between 1 and 10% w/w.

[00012] In an embodiment of the invention, the enteric coat is Sureteric YAE-6-18107 White.

[00013] In an embodiment of the invention, the amount of Sureteric YAE-6-18107 White is between 1 and 20% w/w.

[00014] In a second aspect, the invention provides a pre-blend for the manufacture of a pyridoxal-5'-phosphate oral dosage form comprising: pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof and microcrystalline cellulose, wherein the pre-blend contains an amount of pyridoxal-5'-phosphate is greater than or equal to 80% by weight.

[00015] In an embodiment of the invention, the pre-blend contains an amount of microcrystalline cellulose is greater than or equal to 10% by weight.

[00016] In an embodiment of the invention, the pre-blend comprises about 84.8% w/w of pyridoxal-5'-phosphate of a pharmaceutically acceptable salt and about 15.2% w/w microcrystalline cellulose.

[00017] In a third aspect, the present invention provides a method of preparing the pharmaceutical composition comprising pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof, a disintegrant, a binding agent, and a lubricant wherein the composition contains an amount of pyridoxal-5'-phosphate of at least 50% w/w, the method comprising the steps of: (1) granulating the pyridoxal 5'-phosphate or the pharmaceutical salt thereof, with the disintegrant, the binding agent, and the lubricant to provide a tableting preparation; and (2) compressing the tableting preparation into a core.

[00018] In an embodiment of the invention, step(1) of the method further comprises blending the disintegrant, the binding agent, and the lubricant with a glidant and an anti-adherent.

[00019] In an embodiment of the method of the invention, the disintegrant is croscarmellose sodium; the binding agent is a povidone and microcrystalline cellulose, the lubricant is magnesium stearate, the glidant is colloidal silicon dioxide and the anti-adherent is talc.

[00020] In a further embodiment of the method of the invention, step (1) comprises the steps of: (a) dissolving 1 to 10 % w/w of the povidone in purified water to provide a granulating solution; (b) mixing 50 to 80% w/w of the pyridoxal-5'-phosphate or pharmaceutically acceptable salt with 2 to 15% w/w of a first amount of microcrystalline cellulose to provide a pre-blend; (c) mixing the pre-blend with the granulating solution to provide a first preparation; (d) substantially drying the first preparation; (e) mixing 2 to 15% of a second amount of the microcrystalline cellulose, 3.0% w/w of the croscarmellose sodium, 1 to 5% w/w of the talc and 0.1 to 3% w/w of a glidant to provide a second preparation; and (f) mixing the first and second preparation with 1 to 2% w/w of the magnesium stearate to provide the tableting preparation.

[00021] In a still further embodiment of method of the invention, the amount of povidone is about 4.7% w/w; the amount of pyridoxal 5'-phosphate is about 66.3% w/w; the first amount of the microcrystalline cellulose is about 11.9% w/w; the amount of croscarmellose sodium is about 3.0% w/w; the second amount of the microcrystalline cellulose is about 10.3% w/w; the amount of the croscarmellose sodium is about 3.0%; the amount of magnesium stearate is about 1.1% w/w, the amount of talc is about 2.3% w/w; and the amount of colloidal silicon dioxide is about 0.6% w/w.

[00022] In an embodiment of the method of the invention, the method further comprises the steps of: (3) applying a sealing coat to the core to provide a sealed core; and (4) applying an enteric coat to the sealed core.

[00023] In an embodiment of the method of the invention, the sealing coat is Opadryl-IR-7000 White.

[00024] In an embodiment of the method of the invention, the Opadryl-IR-7000 White is applied as a 15% w/w dispersion.

[00025] In an embodiment of the method of the invention, the enteric coat is Sureteric YAE-6-18107 White.

[00026] In an embodiment of the method of the invention, the Sureteric YAE-6-18107 White is applied as a 15% w/w dispersion.

[00027] In a fourth aspect, the present invention provides a method of reducing the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof, said method comprising the step of administering an effective amount of the pharmaceutical composition according to the invention, said pharmaceutical composition comprising pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof, a disintegrant, a binding agent, and a lubricant, wherein the composition contains an amount of pyridoxal-5'-phosphate of at least 50% w/w.

Brief Description of the Figures

[00028] Figure 1 is a flow chart illustrating the granulation steps in the preparation of pyridoxal 5'-phosphate containing cores for the production of enteric coated tablets.

[00029] Figure 2 is a flow chart illustrating the steps in coating the cores for the production of enteric coated tablets.

[00030] Figure 3 is a line graph illustrating the mean pyridoxal 5'-phosphate plasma concentration following a single oral does of a 15, 30, and 60 mg/kg of an enteric coated formulation of pyridoxal 5'-phosphate.

[00031] Figure 4 is a line graph illustrating individual pyridoxal 5'-phosphate plasma concentration upon multiple dosing at 60 mg/kg daily of an enteric coated formulation of pyridoxal 5'-phosphate over a period of seven days.

[00032] Figure 5 is a line graph illustrating individual pyridoxal 5'-phosphate plasma concentration upon multiple dosing at 30 mg/kg daily of an enteric coated formulation of pyridoxal 5'-phosphate over a period of seven days.

[00033] Figure 6 is a line graph illustrating the mean pyridoxal 5'-phosphate plasma concentration following the seventh dose of a 30 mg/kg an enteric coated formulation of pyridoxal 5'-phosphate.

[00034] Figure 7 is a line graph comparing the mean pyridoxal 5'-phosphate plasma concentration following the seventh dose at 30mg/kg daily of an enteric coated formulation of pyridoxal 5'-phosphate and the individual single-dose plasma profiles at 15, 30 and 60 mg/kg.

Detailed Description

[00035] **Definitions**

[00036] The term "percentage weight per weight (% w/w)" refers to the weight percentage of the particular compound or excipient relative to the total weight of the composition of which the compound or excipient is a constituent of.

[00037] The term "percentage weight per volume (% w/v)" refers to the weight percentage of the particular compound or excipient relative to the total volume of the solution of which the compound or excipient is a constituent of.

[00038] The term "particulate" refers to a state of matter that is characterized by the presence of discrete particles, pellets, beads, or granules irrespective of their size, shape, or morphology.

[00039] The term "multiparticulate" as used herein means a plurality of discrete, or aggregated, particles, pellets, beads, granules, or mixtures thereof irrespective of their shape, size, or morphology.

[00040] The terms "binding agent" or "binder" as used herein means any substance that helps hold a tablet together. A binding agent" or "binder" includes any substance used to cause adhesion of powder particles in tablet granulations.

[00041] The term "lubricant" as used herein means any substance used in tablet formulations to reduce friction during tablet compression. The term "lubricant" also includes any substance which permits the compressed tablet to be properly ejected from a tableting machine.

[00042] The term "glidant" as used herein means any substance used in tablet formulations to reduce friction during tablet compression or any substance which are used to facilitate the flow of the powders in the tableting process.

[00043] The term "anti-adherent" as used herein means any substance which prevents the sticking of tablet formulation ingredients to punches and dies in a tableting machine during production.

[00044] The term "exicipient" as used herein means any inert substance combined with an active drug in order to produce a drug dosage form.

[00045] The term "colorant" as used herein means any substance used to impart color to pharmaceutical preparations (e.g., tablets).

[00046] The terms "sub-coat", "seal coat" or "sealing coat" as used herein refers to any protective coating and include coatings which are moisture or solvent resistant.

[00047] The terms "enteric coat" or "enteric coating" as used herein, means any coating or shell placed on a tablet that breaks up and releases the drug or active ingredient into the intestine rather than the stomach.

[00048] Use of the pharmaceutical composition according to the invention facilitates patient compliance. It is well known that there is an inverse relationship between patient compliance and the frequency of the intake of the medication. The higher the frequency of intake of a prescribed medication, the lower the rate of compliance. It is also known that patient compliance is decreased where the prescribed medication is difficult to administer and consumption of the medication is associated with physical discomfort. The pharmaceutical compositions according to the invention promote patient compliance as the compositions provide high doses of pyridoxal 5'-phosphate in a single or twice daily oral dosage form which is sized for easily swallowing.

[00049] A limiting factor in the tolerance to high doses of pyridoxal 5'-phosphate is gastrointestinal discomfort characterized mainly by nausea and vomiting. The present invention provides novel pharmaceutical compositions suitable for the oral administration of high doses of pyridoxal 5'-phosphate with minimal gastrointestinal side effects. Furthermore, controlled release assists in maintaining a therapeutic concentration of drug in the body for an extended period of time by controlling its rate of delivery.

[00050] The term "disintegrant" as used herein means any substance used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved.

[00051] The present invention provides a pharmaceutical composition capable of delivering high doses of pyridoxal 5'-phosphate comprising pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof, a disintegrant, a binding agent, a lubricant, a glidant, and an anti-adherent, wherein the composition contains an amount of pyridoxal-5'-phosphate of at least 50% w/w. In a preferred embodiment, the pharmaceutical composition comprises an amount of pyridoxal 5'-phosphate of between 50 and 80% w/w and more preferably about 60% w/w.

[00052] Prior art formulations currently available, generally deliver up to 50 mg of pyridoxal 5'-phosphate per dosage form. Accordingly, the prior art formulations must be administered two, three or more times per day to achieve the desired therapeutic levels of pyridoxal 5'-phosphate. In contrast, the pharmaceutical composition of the present invention has a high proportion of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof.

[00053] An individual dosage form of the pharmaceutical composition may contain between 250 and 1000 mg of pyridoxal 5'-phosphate. The pharmaceutical composition according to the invention is suitable for once or twice daily administration.

[00054] The high proportion of pyridoxal 5'-phosphate or its salt allows the pharmaceutical composition to be provided in a dosage form which is smaller in size than the dosage forms of prior art formulations. Thus, the pharmaceutical composition according to the invention is easy to administer and are especially useful for patients who find it difficult to swallow large tablets or capsules.

[00055] The pharmaceutical composition according to the invention may be prepared using either pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof. Both the monohydrate and the anhydrous forms of pyridoxal 5'-phosphate are suitable for preparation of the pharmaceutical compositions of the invention. The pyridoxal 5-phosphate may be provided as salt forms with

pharmaceutically compatible counterions such as but not limited, to citrate, tartate, bisulfate, etc. The pharmaceutically compatible salts may be formed with many acids, including but, not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. The salt forms tend to be more soluble in aqueous or other protonic solvents than the corresponding free base forms.

[00056] Preferably the disintegrant is croscarmellose sodium. The croscarmellose sodium may constitute about to 2 to 10% w/w of the pharmaceutical composition. Preferably the binding agent is microcrystalline cellulose and a povidone. The microcrystalline cellulose is preferably a microcrystalline cellulose having a particle size of about 0.100 mm such as, but not limited to, Avicel PH 102. The microcrystalline cellulose may constitute about 4 to 30 % w/w of the pharmaceutical composition. The povidone is preferably a povidone having a K value of 27-30 such as PVP K30. The lubricant may be magnesium stearate. The anti-adherent may be talc. The glidant may be colloidal silicon dioxide.

[00057] In a preferred embodiment, the pharmaceutical composition comprises between 1 to 10% w/w of povidone, 2 to 10% w/w croscarmellose sodium, 1 to 2% w/w magnesium, 1 to 5% w/w talc and 0.1 to 3% w/w colloidal silicon dioxide.

[00058] In a further preferred embodiment of the invention, the pharmaceutical composition comprises about 66.3% w/w pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof; about 22.2% w/w microcrystalline cellulose; about 3.0% croscarmellose sodium, about 4.7% w/w povidone, about 1.1% w/w magnesium stearate; 2.3% w/w talc; and about 0.6% w/w colloidal silicon dioxide.

[00059] The pharmaceutical composition according to the invention may further comprise additional pharmaceutically acceptable carriers, dispersants and excipients. Suitable excipients include fillers such as sugars, including lactose,

sucrose, mannitol, or sorbitol, or cellulose preparations such as, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone. Disintegrating agents may include cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. The pharmaceutical composition also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Further excipients may comprise anti-adhesives such as talc, colloidal silicon dioxide, titanium dioxide, calcite, microcrystalline cellulose, metallic stearates, and barium sulphates. The composition can also include a granulation binder such as, but limited to, alginic acid.

[00060] A sealing coat or sub-coat protects the tablet ingredients from the water in the aqueous enteric coating dispersion to assure the stability of the dosage form. The sub-coat comprises a resin such as shellac, zein, and the like and is applied to the dosage form by well known methods. Sub-coats used in sugar coating processes usually consist of alcoholic solutions (approximately 10-30% solids) of resins such as shellac, zein, cellulose acetate phthalate, or polyvinyl acetate phthalate. Shellac is preferably used in the form of a shellac-based formulation containing polyvinylpyrrolidone. Other suitable polymeric solutions can be used as a sub-coat, such as Opadry® IR-7000 White or a copolymer of dimethylaminoethyl methacrylate and methacrylic acid ester (Eudragit®).

[00061] Materials useful for preparing enteric coatings for pharmaceuticals are well-known. These most commonly are pH-sensitive materials which are relatively insoluble and impermeable at the pH of the stomach, but which are more soluble and permeable at the pH of the small intestine and colon. Any coating material which modifies the release of the active ingredient in the desired manner may be used. In particular, coating materials suitable for use in the

practice of the invention include but are not limited to polymer coating materials, such as cellulose acetate phthalate, cellulose acetate trimaletate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, ammonio methacrylate copolymers such as Eudragit® RS and RL, poly acrylic acid and poly acrylate and methacrylate copolymers such as Eudragit® S and L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, shellac; hydrogels and gel-forming materials, such as carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium carmellose, sodium carboxymethyl starch, polyvinyl alcohol, hydroxyethyl cellulose, methyl cellulose, gelatin, starch, and cellulose based cross-linked polymers in which the degree of crosslinking is low so as to facilitate adsorption of water and expansion of the polymer matrix, hydoxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin, arninoacryl-methacrylate copolymer (Eudragit® RS-PM), pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, polyvinylpyrrolidone, anionic and cationic hydrogels, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers of maleic anhydride and styrene, ethylene, propylene or isobutylene, pectin, polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, polyethylene oxides, diesters of polyglucan, crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, sodium starch glucolate; hydrophilic polymers such as polysaccharides, methyl cellulose, sodium or calcium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro cellulose, carboxymethyl cellulose, cellulose ethers, polyethylene oxides, methyl ethyl cellulose, ethylhydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate, gelatin, collagen, starch, maltodextin, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of methacrylic acid or methacrylic acid (e.g. Eudragit®), other acrylic acid derivatives, sorbitan esters, natural gums, lecithins, pectin, alginates, ammonia alginate, sodium, calcium, potassium alginates, propylene glycol alginate, agar, and gums such as arabic, karaya, locust bean, tragacanth, carrageens, guar, xanthan, scleroglucan and

mixtures and blends thereof. The thickness of the coating is adjusted to give the desired delay property. In general, thicker coatings are more resistant to erosion and, consequently, yield a longer delay.

[00062] In an embodiment of the invention, the pharmaceutical composition is in the form of a tablet comprising: (a) a core, wherein said core comprises the pyridoxal-5'-phosphate or pharmaceutically acceptable salt thereof, the disintegrant, the binding agent, the lubricant, the glidant and the anti-adherent; (b) a sealing coat surrounding the core; and (c) an enteric coat surrounding the sealing coat.

[00063] The sealing coat and the enteric coat ensure that the core containing the pyridoxal 5'-phosphate is able to pass through the stomach intact and be selectively absorbed in the intestine. The enteric coat is pH dependent and is preferentially souble in the relatively alkaline conditions of the intestine as opposed to the acidic conditions of the stomach. The sealing coat prepares the tablet core surface for the application of the enteric coating to ensure maximum efficiency of the enteric coating with minimal disintegration of the core in the stomach. Sealing and enteric coats are well known in the art. Any suitable combination of sealing and enteric coats can be used to prepare the pharmaceutical compositions according to the invention so long as dissolution of the pyridoxal 5'- phosphate core is preferentially limited to the intestine. In a preferred embodiment of the invention, the sealing coat is Opadryl IR-7000 White and constitutes between 1 and 10% w/w and preferably, about 3.1% w/w of the total composition. The enteric coat is preferably Sureteric YAE-6- 18107 White and constitutes about 1 to 20% w/w and preferably, 10.2 % w/w of the total composition.

[00064] The absorption of the coated embodiments of the pharmaceutical compositions is preferentially limited to the intestine. The pharmaceutical compositions selectively and efficiently dissolve in the relatively alkaline environment of the intestine. Preferably, the pharmaceutical compositions have

a dissolution profile of greater than 80%, and more preferably a dissolution profile of greater than 90%, at 45 minutes according to the United States Pharmacopoeia dissolution test in a 0.05M phosphate buffered solution having a pH of 6.8. Absorption of the pharmaceutical compositions in the stomach is minimal. The structural integrity of the coated embodiments of the pharmaceutical compositions of the invention is minimally affected by the acidic conditions of the stomach. Preferably, the pharmaceutical compositions have a dissolution profile of less than 10% and more preferably, a dissolution profile of less than 1% at 120 minutes according to the United States Pharmacopoeia dissolution test in 0.1N HCl.

[00065] The pharmaceutical compositions according to the present invention provide improved pyridoxal 5'-phosphate bioavailability. Preferably, *in vivo* oral intake of between 15 and 60 mg/kg of the composition produces an average plasma level of between 0.1 and 2 mg/l of pyridoxal 5'phosphate in the period from 2 hours after intake to 24 hours after intake. *In vivo* oral intake of between 15 and 60 mg/kg of the composition preferably produces a maximum plasma level (Cmax) of pyridoxal 5'-phosphate of between 2 and 6 mg/l.

[00066] In a second aspect, the present invention provides a pre-blend useful in the manufacture of a pyridoxal 5'-phosphate oral dosage form. Powdered preparations of pyridoxal-5'-phosphate suffer poor flowability. As a consequence, it is difficult to prepare tablets of pyridoxal 5'-phosphate in a consistent manner. Because powdered pyridoxal 5'-phosphate does not tend to disperse evenly, it is difficult to uniformly blend and granulate pyridoxal 5'-phosphate with other ingredients (i.e. exicipients) prior to tableting.

[00067] Where it is desirable to produce a tablet having a high concentration of pyridoxal 5'-phosphate, it is necessary to granulate the pyridoxal 5'-phosphate in order to alter its physical properties into a material that can flow. Good flow properties are essential for tableting since the powder has to be able to flow into the die cavity in which the tablet will be formed with punches. If the powder

does not flow evenly and quickly, it is difficult to control tablet weights. Poor flow properties also necessitates the use of very slow compression speeds which are impractical for commercial purposes.

[00068] The present invention provides a pre-blend comprising pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, wherein the pre-blend contains an amount of pyridoxal 5'-phosphate is greater than or equal to 80% by weight. The flow characteristics of the pre-blend, as compared to powdered pyridoxal 5'-phosphate alone, allows for improved ease in handling and in blending the active ingredient with other ingredients such as but not limited to disintegrants, binding agents, lubricants.

[00069] In a preferred embodiment, the pre-blend comprises an amount of microcrystalline cellulose of at least 10% by weight. In a further preferred embodiment, the pre-blend comprises about 84.8% w/w of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof and 15.2 %w/w of microcrystalline cellulose. In yet a further preferred embodiment, the microcrystalline cellulose is a microcrystalline cellulose having a particle size of about 0.100 mm such as but not limited to, Avicel PH 102.

[00070] The pre-blend according to the invention is especially usefully for in the manufacture of oral dosage forms of pyridoxal 5'-phosphate such as tablets and capsules.

[00071] In a third aspect, the invention provides a method of preparing the pharmaceutical composition according to the invention which comprises pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof, a disintegrant, a binding agent, a lubricant, a glidant and an anti-adherent wherein the composition contains an amount of pyridoxal-5'-phosphate of at least 50% w/w. The method comprises the steps of: (1) granulating the pyridoxal 5'-phosphate or the pharmaceutical salt thereof, with the disintegrant, the binding

agent, the lubricant, the glidant, and the anti-adherent to provide a tableting preparation; and (2) compressing the tableting preparation into a core.

[00072] In a further embodiment, step (1) of the method comprises the steps of: (a) dissolving 1 to 10 % w/w of the povidone in purified water to provide a granulating solution; (b) mixing 50 to 80% w/w of the pyridoxal-5'-phosphate or pharmaceutically acceptable salt with 2 to 15% w/w of a first amount of microcrystalline cellulose to provide a pre-blend; (c) mixing the pre-blend with the granulating solution to provide a first preparation; (d) substantially drying the first preparation; (e) mixing 2 to 15% of a second amount of the microcrystalline cellulose, 3.0% w/w of the croscarmellose sodium, 1 to 5% w/w of the talc and 0.1 to 3% w/w of a glidant, to provide a second preparation; and (f) mixing the first and second preparation with 1 to 2% w/w of the magnesium stearate to provide the tableting preparation.

[00073] In a preferred embodiment of the invention, step (a) comprises the step of dissolving about 4 7% w/w of the povidone in purified water to provide the granulating solution. The povidone is preferably a povidone having a K value of between 27 and 30 and is more preferably PVP K30.

[00074] In the preferred embodiment of the invention, step (b) comprises the preparation of a pyridoxal 5'-phosphate containing pre-blend by mixing about 66.3 % w/w of the pyridoxal-5'-phosphate (or a pharmaceutically acceptable salt thereof) powder with about 11.9% w/w of a first amount of the microcrystalline cellulose. The microcrystalline cellulose may preferably be a microcrystalline cellulose having a particle size of about 0.100mm, and more preferably the microcrystalline cellulose is Avicel PH102. The pre-blend can be mixed using a ribbon blender.

[00075] In the preferred embodiment of the invention, step (c) comprises mixing the pre-blend with the granulating solution to provide a first preparation using a ribbon blender.

[00076] In the preferred embodiment, step (d) comprises the wet first preparation is then substantially dried using a forced air drying oven set at 45°C. In some circumstances, it may be desirable to size the first preparation after drying, by passing it through a 12 mesh screen.

[00077] In the preferred embodiment, step (e) comprises the provision of a second preparation by mixing about 10.3% w/w of a second amount of the microcrystalline cellulose, about 3.0% w/w of the croscarmellose sodium, about 2.3% w/w of the talc as the anti-adherent, and about 0.6% w/w of the colloidal silicon dioxide as the glidant. In some circumstances, it may be desirable to size the second granulation preparation by passing it through a 16 mesh screen.

[00078] In the preferred embodiment, step (f) comprises mixing together the first and second preparation with about 1.1% w/w of the magnesium stearate, to provide the tableting preparation using a diffusive blender.

[00079] Step (2) of the method, compression of the tableting preparation into tablets, can be accomplished using tableting methods and apparatus known in the art. Preferably, the tablets are prepared using a rotary tablet press and plain, round, standard, concave, 11mm tablet tool.

[00080] In another embodiment of the invention, the method for preparing the pharmaceutical compositions according to the invention further comprises following steps (1) and (2), the steps of: (3) applying a sealing coat to the core to provide a sealed core; and (4) applying an enteric coat to the sealed core.

[00081] Preferably, the sealing coat is applied as a 15% w/w dispersion of Opadryl-IR-7000 White and the enteric coat is applied as 15% w/w dispersion of Sureteric YAE-6-18107 White. A side vented perforated coating pan or other suitable device can be used to apply the coatings by conventional methods.

[00082] In a fourth aspect, the present invention further provides a method of reducing the incidence of nausea and vomiting associated with the oral

administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof, said method comprising the step of administering an effective amount of pyridoxal 5'-phosphate in a controlled release, delayed release, or a combination of a controlled release and delayed released oral pharmaceutical composition.

[00083] By controlled release is meant any formulation technique wherein release of the active substance from the dosage from is modified to occur at a slower rater than that from an immediate release product, such as a conventional swallow tablet or capsule.

[00084] By delayed release is meant any formulation technique wherein release of the active substance from the dosage form is modified to occur at a later time than that from a conventional immediate release product. The subsequent release of active substance from a delayed release formulation may also be controlled as defined above.

[00085] Such controlled release formulations are preferably formulated in a manner such that release of the pyridoxal 5'-phosphate is effected predominantly during the passage through the stomach and the small intestine, and delayed release formulations are preferably formulated such that release of active substance is avoided in the stomach and is effected predominantly during passage through the small intestine. The small intestine is suitably the duodenum, the ileum or the jejunem.

[00086] In a preferred embodiment, the controlled release or delayed release pharmaceutical composition is a pharmaceutical composition according to the invention, comprising: pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof, a disintegrant, a binding agent, a lubricant, a glidant and an anti-adherent, wherein the composition contains an amount of pyridoxal-5'-phosphate of at least 50% w/w, wherein the composition is in the form of a tablet comprising: (a) a core, wherein said core comprises the pyridoxal-5'-phosphate, the disintegrant, the binding agent, the lubricant, the glidant and the

anti-adherent; (b) a sealing coat surrounding the core; and (c) an enteric coat surrounding the seating coat.

[00087] In a further preferred embodiment, the controlled release or delayed release pharmaceutical composition is a pharmaceutical composition according to the invention, comprising: about 66.3% w/w pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof; about 3.0% w/w croscarmellose sodium as the disintegrant; about 4.7% w/w povidone and about 22.2% w/w microcrystalline cellulose as the binding agent, about 1.1% w/w magnesium stearate as the lubricant , about 2.3% talc as the anti-adherent, and about 0.6% colloidal silicon dioxide as the glidant.

[00088] Any of the coated pharmaceutical compositions of the invention can be used to reduce the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof.

[00089] The pharmaceutical compositions generally are administered in an amount effective for treatment or prophylaxis of a specific indication or indications. It is appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, route of administration, complicating conditions and the like. A therapeutically effective dose further refers to that amount of the compound sufficient to result in amelioration of symptoms associated with such disorders. Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., latest edition. For administration to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be 100 to 1000 mg, typically around 500 mg. The physician in any event may determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The above dosages are exemplary of the average case.

There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[00090] Although the invention has been described with reference to illustrative embodiments, it is to be understood that the invention is not limited to these precise embodiments, and that various changes and modifications may be effected therein by one skilled in the art. All such changes and modifications are intended to be encompassed in the appended claims.

[00091] **Example One – Pyridoxal 5'-phosphate Enteric Coated Tablet Formulation and Method of Preparation**

[00092] Table 1 sets out the ingredients and relative amounts for the preparation of enteric coated tablets of pyridoxal 5'-phosphate (265 mg per tablet). As set out in table 1, one batch yields 20,000 tablets. The batch size can be scaled up or down by increasing or decreasing the relative amounts proportionately.

Table 1: Formulation for Enteric Coated Pyridoxal 5'-phosphate Tablets

Ingredient	% w/w	mg/tablet	g/batch
Granulation Phase			
Pyridoxal 5'-phosphate Powder	66.3	265	5300
Microcrystalline Cellulose (Avicel PH102)	11.9	47.5	950
Povidone (K-30)	4.7	18.75	375
Sub-Total:	**82.8**	**331.25**	**6625**
Purified Water (for PVP granulation solution)		qs	1500
Additional Purified Water (for granulation)		qs	150
Tableting Phase			
Granulation	82.8	331.25	6625
Microcrystalline Cellulose (Avicel PH102)	10.3	41	820
Croscarmellose Sodium	3.0	12	240
Talc	2.3	9	180
Colloidal Silicon Dioxide	0.6	2.25	45
Magnesium Stearate	1.1	4.5	90
Total:	**100.0**	**400**	**8000**

Coating Phase			
Opadry-IR-7000 White (Sealing coat)-15% dispersion	3.1	14.1	282
Sureteric YAE-6-18107 White- (Enteric Coat)-15%	10.2	47.1	942
Coated Tablet Total:	**100.0**	**461.2**	
Purified Water (for Sealing coat)		qs	1598
Purified Water (for Enteric Coat)		qs	5338

[00093] The pyridoxal 5'-phosphate enteric coated tablets are prepared in a three step process: (1) granulation and blending phase, (2) tableting phase, and (3) coating phase. Figures 1 and 2 illustrate the steps involved in preparing the tablets.

[00094] **Granulation and Blending Phase** – A granulating solution is prepared by dissolving the Povidone K30 in a suitable amount of purified water. A pyridoxal 5'phosphate pre-blend is prepared by mixing the pyridoxal 5'-phosphate powder with the first amount of microcrystalline cellulose (Avicel PH 102) for approximately 3 minutes in a ribbon blender. While continuing to mix the pre-blend, the granulating solution is added to form granules. Additional water is added as necessary for the granulating process. The pre-blend and the granulation solution are mixed for approximately 5 minutes. The resulting granules are sized by passing the granules through a 12 mesh screen and then placed on paper lined trays. The granules are then dried in a forced air drying oven at 45°C. The dried granules are sized by passing the granules through a 12 mesh screen. The second amount of microcrystalline cellulose (Avicel PH 102), the croscarmellose sodium, the talc, the colloidal silicon dioxide and magnesium stearate mixed and then passed through a 16 mesh screen. The mixture is then combined with the dried and sized granules and mixed using a diffusive blender for approximately 8 minutes to provide the tableting mixture.

[00095] **Tableting phase** –The tableting preparation is compressed into cores using a rotary tablet press and a plain, 11mm, round, standard, concave tablet tool.

[00096] **Coating phase** – The sealing coat is prepared by dispersing the Opadryl Y-IR-7000 in a suitable about of purified water to provide a 15% w/w dispersion. A sufficient amount of the Opadryl Y-IR-7000 dispersion is applied the core such that amount of applied Opadryl Y-IR-7000 is about 3.1% w/w relative to the total weight to the finished tablet. The enteric coating is prepared by dispersing the Sureteric YAE-6-18107 in a suitable amount of purified water to provide a 15% w/w dispersion. A sufficient amount of the Sureteric YAE-6-18107 is applied such that the amount of Sureteric YAE-6-18107 is about 10.2 % w/w relative to the total weight of the finished tablet. Using a side vented perforated coating pan, the tablet cores are first coated with the sealing coat dispersion. The tablets are then coated with the enteric coat dispersion.

[00097] **Example Two – Stability and Dissolution Analysis of Pyridoxal 5'-phosphate Enteric Coated Tablet**

[00098] The dissolution and stability properties of the pyridoxal 5'-phosphate enteric coated tablets were determined using conventional testing methods. The dissolution test was performed in a VanKel Model Vanderkamp 600 (6 spindle) dissolution apparatus equipped with an autosampler, digital thermometer and timer. At the Initial, 0.5, and 1-month testing points, a paddle speed was set up at 75 rpm. After the 3 month testing point, the paddle speed, in view of SUPAC guidelines, was increased to 100 rpm. The sampling volume was 10 ml. A 2-stage dissolution procedure was carried out based on USP 24 <724> method B for enteric coated tablets. The Acid Stage was carried out using 0.1N HCl for 120 minutes at 37°C followed by the buffer stage at pH 6.8 at 37°C.

[00099] At time points Initial, 0.5, and 1-month, storage stability label claim and disintegration data for pyridoxal 5'-phosphate enteric coated tablets were observed within the following specification limits:

- Dissolution in 0.1 N HCl: 120 minutes = not more than 10%

- Dissolution in pH 6.8 buffer: 45 minutes = no individual tablet is less than 60%;

- Dissolution in pH 6.8 buffer: 60 minutes = no individual tablet is less than 60%.

[000100] Pyridoxal 5'-phosphate concentration in the buffer stage dissolution was observed to be reduced by approximately 12% in the one-month sample compared to data from time 0.5 month (at 60 minutes).

[000101] Table 2 summarizes the stability and dissolution profiles at time points: Initial, 0.5, 1, and 3 months.

Test/Method	Limit	Accelerated Studies			
		Initial	0.5 month	1 months	3 months
Appearance	([3])	White, bi-convex tablets	White, bi-convex tablets	White, bi-convex tablets	White, bi-convex tablets
Tablet weight	420 mg - 460 mg	432.9 mg	434.7 mg	435.4 mg	441.08 mg
Disintegration Time USP24<701> in simulated gastric fluid USP (minus pepsin)	Tablets remain intact	5 of 6 tablets - no change 1 of 6 swollen on one edge	5 of 6 tablets - no change 1 of 6 swollen on one edge	4 of 6 tablets - no change 2 of 6 swollen on one edge	4 of 6 tablets - no change 2 of 6 swollen on one edge
USP24<701> in simulated intestinal fluid USP (minus pancreatin)	Run and report	14'00" - 18'15"	11'30" - 14'15"	13'00" - 16'00"	6'19" - 10'38"
Visually observe degree of dispersion of disintegrated tablet	Run and report degree of dispersion	Dissolution of film at edges and sides followed by flow disintegration of the core	Dissolution of film at edges and sides followed by slow disintegration of the core	Dissolution of film at edges and sides followed by slow disintegration of the core	Dissolution of film at edges and sides followed by slow disintegration of the core
Water content	Run and report	1.8%	2.7%	5.3%	2.5%
Dissolution	Run and report[4]	Dissolution in 0.1 N HC1 120 minutes = 0% label claim Dissolution in pH 6.8 buffer 45 minutes = 79.7-116.8% label claim 60 minutes = 101.2-115.3% label claim	Dissolution in 0.1 N HC1 120 minutes = 0.1-0.7% label claim Dissolution in pH 6.8 buffer 45 minutes = 86.8-89.8% label claim 60 minutes = 87.2-91.0% label claim	Dissolution in 0.1 N HC1 120 minutes = 0% label claim Dissolution in pH 6.8 buffer 45 minutes = 67.5-76.5% label claim 60 minutes = 69.8-83.0% label claim	Dissolution in 0.1 N HC1 120 minutes = 0% label claim Dissolution in pH 6.8 buffer 30 minutes = 92.6-94.8% label claim 45 minutes = 93.7-96.3% label claim 60 minutes = 95.2-97.3% label claim

Test/Method	Limit	Accelerated Studies			
		Initial	0.5 month	1 months	3 months
Uniformity of dosage units	85-115% (w/w) of label claim	97.2%	95.8%	97.0%	97.0%
Assay content of MC-1 and related substances	Release: 225-276 mg	247.3 mg/tablet	242.1 mg/tablet	245.3 mg/tablet	245.3 mg/tablet
Assay content related substances	Shelf life stability in progress	not detected	not detected	not detected	not detected

[3] Plain white to off-white film-coated bi-convex tablets.
[4] After the two month stability testing point speed of the apparatus has been changed from 75 to 100 RPM (see dissolution summary)

[000102] **Example Three — Bioavailability Analysis for Pyridoxal 5'-phosphate Enteric Coated Tablet, Single Dose and Multiple Doses**

[000103] **Pharmacokinetics Study** - The protocol was designed to first study a single dose of pyridoxal 5'-phosphate at three different dose levels: 15, 30 and 60 mg/kg of body weight. Following evaluation of safety and tolerance, the highest tolerated dose was administered once daily for seven consecutive days. The product was manufactured as enteric-coated tablets each containing 250 mg of pyridoxal 5'-phosphate. The dose was calculated based on the body weight and rounded to the nearest 250 mg.

[000104] During the single-dose phase, blood samples were collected prior to dosing and 1, 2, 3, 4, 5, 6, 7, 8, 12, 16 and 24 hours following drug administration. During the multi-dose phase, blood samples were drawn each morning prior to dosing and 2 hours post-dose. Following the last dose on day 7, blood samples were drawn after 1, 2, 3, 4, 5, 6, 7, 8, 12, 16 and 24 hours.

[000105] All samples were constantly protected from ultraviolet light, collected in pm-cooled blood collection tubes and kept in an ice bath until centrifugation within twenty minutes of their collection. Plasma samples were separated and divided into two approximately equal aliquots and stored at -70 ± 10°C pending shipment (over dry ice) to the analytical laboratory.

[000106] **Electrocardiograms** - For the single-dose study, electrocardiograms (ECG's) were recorded prior to dosing and 1, 2 and 12 hours following drug administration. All ECG's were to be recorded within± 15 minutes of the scheduled time.

[000107] **Vital Signs** - Blood pressure, heart rate, respiratory rate and oral body temperature were recorded every day prior to drug administration and 1, 2, 6 and 12 hours post-dose. All vital signs were to be measured within± 15 minutes of their scheduled time.

[000108] **Pharmacokinetic Analysis** - The following pharmacokinetic parameters were calculated: area under the curve from time zero to the last measurable concentration (AUC-T), area under the curve from time zero to infinity (AUC-inf), maximal plasma concentration (Cmax), time of maximal plasma concentration (Tmax), elimination constant (Kel), half-life (T½), mean residence time (MRT), clearance (Cl) and volume of distribution (Vd).

[000109] Whenever possible, the area under the plasma concentration-time curve was calculated from time zero to the last measurable concentration (AUC T) using the linear trapezoidal method. AUC-T is expressed as ng.h/ml. AUC-T was also normalized for body weight and expressed as ng.h/ml/kg.

[000110] The area under the curve from time zero to infinity (AUC-inf) was calculated as the sum of AUC-T + Clast/Kel where Clast represents the last measurable concentration and Kel the elimination rate constant calculated by linear least squares regression using the data points that best represent the terminal linear phase. AUC-inf is expressed as ng.h/ml. AUC-inf was also normalized for body weight and expressed as ng.h/mg/kg.

[000111] Cmax was defined as the highest observed plasma concentration over the 24-hour collection period. Cmax is expressed in ng/ml. Cmax was also normalized for body weight and expressed as ng/ml/kg.

[000112] Tmax, was defined as the time where the maximal plasma concentration was reached.

[000113] The oral clearance was evaluated by dividing the dose (mg/kg) by AUC-inf (ng.h/mL). Clearance is expressed as L/h/kg. The actual clearance was also calculated without normalization for body weight and expressed as L/h.

[000114] The volume of distribution is actually the Vd_{area} calculated by dividing the clearance (L/h/kg) by Kel (h-1). Vd is expressed as L/kg and is not

corrected for absolute bioavailability. The actual volume of distribution was also calculated without normalization for body weight and expressed in liters.

[000115] The mean residence time (MRT) was defined as the quotient of the area under the first moment curve and AUC-inf. The product of concentration by time is plotted versus time and the area under the first moment curve is calculated. The results are expressed in hours.

[000116] **Dose Calculation** - The dose was calculated based on the body weight and the total dose was rounded to the nearest 250 mg to determine the number of tablets to administer. Descriptive statistics reveal that the actual dose was relatively close to the theoretical dose.

[000117] Subjects randomized to the 15 mg/kg group actually received a dose of 14.58 ± 1.11 mg/kg. Those assigned to the 30-mg dose received 30.52 ± 1.44 mg/kg. Subjects in the 60-mg/kg group actually received 59.87 ± 0.91 mg/kg. During the multi-dose phase of the study, the number of tablets was calculated prior to the first drug administration and remained constant throughout the duration of the study, regardless of any change in body weight. Subjects who were to receive 30 mg/kg for seven days actually received 29.93 ± 1.07 mg/kg.

[000118] **Single Dose Pharmacokinetics** - Figure 3 illustrates the mean plasma concentration following each dose. The pharmacokinetic parameters are summarized in Table 2.

Table 2: Summary of Pharmacokinetic Parameters, Single Phase Dose

DOSE (mg/kg)	15 MG/KG	30 MG/KG	60 MG/KG
NUMBER OF SUBJECTS	4-6	5-6	6
AUC-T (ng.h/ml)	12036 ± 10489	25978 ± 45083	18685 ± 17831
AUC-INF (ng.h/ml)	21635 ± 11963	34571 ± 50484	22503 ± 17036
CMAX (ng/ml)	2837 ± 2987	6426 ± 12423	4466 ± 5102

Lag time (h)	4.5 ± 2.4	2.7 ± 1.0	2.2 ± 1.2
TMAX (h)	7.0 ± 2.8	4.3 ± 1.2	4.5 ± 0.5
T1/2 (h)	10.0 ± 4.9	20.2 ± 15.6	15.3 ± 6.3
MRT (h)	15.2 ± 5.5	11.2 ± 6.1	12.1 ± 2.9
CI (L/h)	66 ± 45	128 ± 69	250 ± 123
Vd (L)	2440 ± 2898	2876 ± 2269	6103 ± 3881

Results are expressed as mean ± standard deviation

[000119] As illustrated in Figure 3, following a single dose of pyridoxal phosphate at 15 mg/kg, a mean maximal plasma concentration of 1870 ± 2652 ng/ml was reached after 6 hours. After a single dose of 30 mg/kg, a mean maximal plasma concentration of 5563 ± 12820 ng/ml was reached after 3 hours. Following a single dose of 60 mg/kg, the mean maximal plasma concentration reached 3922 ± 5457 ng/ml after 4 hours.

[000120] Examination of the individual curves reveals that the pharmacokinetics of pyridoxal 5'-phosphate is characterized by a large variability. For instance, subject # 11 in the 30-mg/kg group reached a maximal plasma concentration of 31,719.5 ng/ml after 3 hours compared to the group average of 5563 ng/ml at 6 hours. Subject # 01 and 02 in the 15-mg/kg group had very different maximal plasma concentration. The plasma profile of subject # 01 peaked at 6238 ng/ml after 4 hours compared to subject # 02 whose whole plasma peak occurred at 132 ng/ml 12 hours post-dose. As shown in Table 2, coefficients of variation varying form 50 to 200% are not unusual.

[000121] **Multiple Dose** - Based on the safety and tolerance profile observed during the single-dose phase of the study, a dose of 60 mg was selected for the multi-dose phase. However, upon multiple dosing, gastrointestinal intolerance developed during the first few days and subjects were dosed for the last time on Day 3. The multi-dose phase was reinitiated using the next highest dose, 30 mg/kg. All subjects completed this part of the study.

[000122] For subjects who participated to the first multi-dose phase at 60 mg/kg, the pre-dose and two-hour post-dose plasma concentrations are summarized in Table 3 and illustrated in Figure 4.

Table 3: Plasma Concentration Upon Multiple Dosing At 60 mg/kg

Day	Pre-dose (ng/ml)	2 hours post-dose (ng/ml)
1	0 ± 0	129 ± 273
2	327 ± 197	288 ± 149
3	237 ± 117	219 ± 102
4	364 ± 157	---

Results are expressed as mean ± standard deviation.

[000123] Apparent missing data points in Figure 4 are actually samples below the lower limit of quantitation (50 ng/ml). The lag time previously observed with the single-dose administration could possible explain the lower concentration two hours post-dose compared to the pre-dose.

[000124] Table 4 summarizes the descriptive statistics for the second multi-dose phase carried out with an oral dose of 30 mg/kg.

Table 4: Plasma Concentration Upon Multiple Dosing at 30 mg/kg

Day	Pre-dose (ng/ml)	2 hours post-dose (ng/ml)
1	9 ± 23	1641 ± 3590
2	147 ± 49	1558 ± 3390
3	213 ± 73	2010 ± 4352
4	342 ± 167	336 ± 187
5	202 ± 75	1477 ± 2878
6	290 ± 148	287 ± 88
7	244 ± 101	642 ± 924

Results are expressed as mean ± standard deviation

[000125] Individual daily plasma concentrations are presented in Figure 5 and illustrate the large intersubject variability. Subject # 21 represents a case where the absorption is particularly important although her pre-dose plasma concentration is similar to that of the other subjects.

[000126] These results were submitted to an analysis of variance where the terms of the model included subjects and day of treatment. The pre-dose plasma concentration is significantly different between days ($p = 0.0011$). No significant difference was observed between days with regard to the plasma concentration two hours post-dose ($p = 0.5284$). The analysis of variance including subjects, days and times as the factors revealed a significant difference between pre-dose and two hours post-dose ($p = 0.0426$).

[000127] **Last Dose of the Multiple Dose (Day 7)** - Table 5 summarizes the pharmacokinetic parameters and Figure 6 illustrates the mean plasma profile. The pharmacokinetic parameters of Table 5 are also characterized by a large variability with coefficients of variation on over 10 The pharmacokinetic parameters calculated on Day 1 were compared to those calculated on Day 7 using an analysis of variance. None of the comparisons revealed a significant difference which would indicate that pyridoxal 5'-phosphate does not accumulate upon multiple dosing, at least at a dose of 30 mg/kg administered as enteric coated tablets.

Table 5: Summary of Calculated Pharmacokinetic Parameters on Day 7 of the Multi-dose Phase at 30 mg/kg

DOSE (mg/kg)	**30 MG/KG**
AUC-T (ng.h/mL)	32173 ± 25942 (5)
AUC-INF (ng.h/mL)	38341 ± 24942 (5)
CMAX (ng/mL)	7966 ± 6831 (5)
TMAX (h)	3.6 ± 0.9 (5)
T1/2 (h)	23.0 ± 28.0 (5)
MRT (h)	11.8 ± 5.3 (5)
CI (L/h)	86 ± 53 (4)
Vd (L)	4148 ± 5560 (4)

Results are expressed as mean ± standard deviation (n)

[000128] Additional evidence that pyridoxal 5'-phosphate does not accumulate upon multiple dosing is provided in Figure 7 where the plasma concentration on the seventh day of dosing at 30 mg/kg is plotted on the same

graph as the three mean plasma profiles following a single dose of 15 and 60 mg/kg.

[000129] **Dose Linearity** - The relationship between the calculated pharmacokinetic parameters and dose was evaluated by submitting the data to a linear regression analysis where each of the parameters was regressed on the dose (expressed either as mg or mg/kg). The pharmacokinetic parameters were uncorrected as well as normalized for body weight. Table 6 summarizes the regression coefficient (R^2), the intercept, the slope and the 95% confidence interval for the slope, for each individual parameter. In these analyzes, the correlation between the uncorrected parameters and the dose expressed in milligrams was evaluated.

Table 6: Summary of Regression Analysis, Parameter = Intercept + Slope x Dose (mg)

PARAMETER	R^2	INTERCEPT	SLOPE	95% CONFIDENCE INTERVAL OF THE SLOPE	
				LOWER LIMIT	UPPER LIMIT
AUC-t (ng.h/ml)	0.0213	12119	2.8298	-7.3291	12.9887
AUC-inf (ng.h/ml)	0.0030	23286	1.0935	-10.3228	12.5097
Cmax (ng/ml)	0.0183	2854	0.7249	-2.0902	3.5400
Cl (L/h)	0.4693	19.78	0.0541	0.0211	0.0871
Vd (ml)	0.1809	1485	0.9921	-0.2182	2.2025
Tmax (h)	0.1853	6.77	0.0006	-0.0013	0.0001
T1/2 (h)	0.0000	15.90	0.00003	-0.0044	0.0043
MRT (h)	0.0860	15.21	0.0010	-0.0028	0.0008

[000130] The regression analysis was also carried out using the normalized parameters (expressed per kg of body weight) and the dose expressed in mg/kg. The results are summarized in Table 7.

Table 7: Summary of Regression Analysis, Parameter = Intercept + Slope x Dose (mg)

PARAMETER	R^2	INTERCEPT	SLOPE	95% CONFIDENCE INTERVAL OF THE SLOPE	
				LOWER LIMIT	UPPER LIMIT
AUC-t (ng.h/ml/kg)	0.0083	207	1.5961	-7.6550	10.8472
AUC-inf (ng.h/ml/kg)	0.0007	385	-0.4816	-10.6671	9.7039
Cmax (ng/ml/kg)	0.0064	49.6	0.3912	-2.1937	2.9761
C1 (L/h/kg)	0.4640	0.2369	0.0571	0.0219	0.0922
Vd (ml/kg)	0.2051	16.67	1.2245	-0.1572	2.6062
Tmax (h)	0.2115	7.0	-0.0495	-0.1002	0.0012
T1/2 (h)	0.0054	14.23	0.0420	-0.2841	0.3681
MRT (h)	0.0512	14.83	-0.0557	-0.1932	0.0818

[000131] **Gender Differences** - The pharmacokinetic parameters calculated during the single-dose phase of the study were compared with regard to gender differences using analyses of variance where the model included dose, gender and the interaction dose by gender. In these analyses, the pharmacokinetic parameters were expressed both its absolute values and normalized per kilogram of body weight. Table 8 summarizes the probability values for the various statistical comparisons.

Table 8: ANOVA Probability Values for Gender Differences Following a Single Dose of 15, 30, or 60 mg/kg.

Parameter	Dose		Gender		Dose x Gender	
	Absolute	Per kg	Absolute	Per kg	Absolute	Per kg
AUC_t	0.7170	0.7339	0.5255	0.6745	0.3381	0.2859
AUC_{inf}	0.5282	0.5536	0.4534	0.6511	0.1109	0.0795
C_{max}	0.7445	0.7802	0.5476	0.6830	0.3371	0.2960
C1	0.0096	0.0205	0.5769	0.9422	0.1494	0.3294
Vdarea	0.1796	0.2640	0.5511	0.3865	0.4480	0.7508
Tmax	0.0462		0.3839		0.5560	

T1/2	0.4238	0.6067	0.9574
MRT	0.3202	0.2606	0.3900

[000132] No significant differences were observed between men and women with regard to any of the pharmacokinetic parameters. The only significant difference was observed between doses for clearance expressed in absolutes units or normalized by body weight. This highly significant difference relates to the weak linear relationship previously observed. The maximal plasma concentration appears to be reached significantly later following the 15 mg/kg dose.

[000133] **Discussion** - Six subjects (three men and three women) were enrolled in each dose level. All of the subjects completed the single-dose phase of the study. Based on the clinical evaluation, the 60-mg/kg dose appeared to be the highest tolerated dose. This dose was therefore selected for the multi-dose administration. Gastrointestinal intolerance developed and the decision to terminate the study was taken during the third day. Subjects were kept under observation and were discharged on the next day. The multi-dose phase was rescheduled for a similar study using a daily dose of 30 mg/kg.

[000134] Enteric-coating the tablets resolved the nausea and vomiting problem observed in the previous study. Subjects could tolerate doses much higher than those used previously.

[000135] There is an absence of accumulation of pyridoxal 5'-phosphate upon multiple dosing. The pre-dose plasma concentration appears to stabilize within one or two days and is maintained approximately between 200 and 300 ng/ml.

What is claimed is:

1. A pharmaceutical composition for oral administration comprising: pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof, a disintegrant, a binding agent, and a lubricant, wherein the composition contains an amount of pyridoxal-5'-phosphate of at least 50% w/w.

2. The pharmaceutical composition according to claim 1, wherein the amount of the pyridoxal 5'-phosphate is between 50 and 80% w/w.

3. The pharmaceutical composition according to claim 1, wherein the amount of the pyridoxal 5'-phosphate is about 60% w/w.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the disintegrant is croscarmellose sodium.

5. The pharmaceutical composition according to claim 4, wherein the amount of croscarmellose sodium is about 2 to 10% w/w.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the binding agent is a povidone.

7. The pharmaceutical composition according to any one of claims 1 to 5, wherein the binding agent is a microcrystalline cellulose.

8. The pharmaceutical composition according to any one of claims 1 to 5, wherein the binding agent is a mixture of a povidone and a microcrystalline cellulose.

9. The pharmaceutical composition accord to claim 7 or 8, wherein the microcrystalline cellulose has a particle size of about 0.100 mm.

10. The pharmaceutical composition according to any one of claims 7 to 9, wherein the microcrystalline cellulose is Avicel PH 102.

11. The pharmaceutical composition according to any one of claims 7 to 10, wherein the amount of microcrystalline cellulose is between about 4 and 30% w/w

12. The pharmaceutical composition according to claims 6 or 8, wherein the povidone has a K value of between 27-33.

13. The pharmaceutical composition according to claims 6 or 8, wherein the povidone is PVP K30.

14. The pharmaceutical composition according to claims 6, 8, 12 or 13, wherein the amount of povidone is between about 1 and 10% w/w.

15. The pharmaceutical composition according to claim 6. 8, 12, 13, or 14 wherein the povidone is in solution.

16. The pharmaceutical composition according to any one of claims 1 to 15, wherein the pharmaceutical composition further comprises a lubricant.

17. The pharmaceutical composition according to claim 16, wherein the lubricant is magnesium stearate.

18. The pharmaceutical composition according to claim 17, wherein the amount of magnesium stearate is between about 1 and 2% w/w.

19. The pharmaceutical composition according to any one of claims 1 to 18, wherein the pharmaceutical composition further comprises a glidant.

20. The pharmaceutical composition according to claim 19, wherein the glidant is colloidal silicon dioxide.

21. The pharmaceutical composition according to claim 20, wherein the amount of the colloidal silicon dioxide is about 0.1 to 3% w/w.

22. The pharmaceutical composition according to any one of claims 1 to 21, wherein the pharmaceutical composition further comprises an anti-adherent.

23. The pharmaceutical composition according to claim 22, wherein the anti-adherent is talc.

24. The pharmaceutical composition according to claim 23, wherein the amount of the talc is about 1 to 5% w/w.

25. The pharmaceutical composition according to claim 24, wherein the composition comprises about 66.3% w/w pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof; about 3.0% w/w croscarmellose sodium as the disintegrant; about 4.7% w/w povidone and about 22.2% w/w microcrystalline cellulose as the binding agent, about 0.6% colloidal silicon dioxide as the glidant, and about 1.1% w/w magnesium stearate as the lubricant and about 2.3% talc as the anti-adherent.

26. The pharmaceutical composition according to any one of claims 1 to 25, wherein the composition is in the form of a tablet comprising: (a) a core, wherein said core comprises the pyridoxal-5'-phosphate or pharmaceutically acceptable salt, the disintegrant, the binding agent, and the lubricant; (b) a sealing coat surrounding the core; and (c) an enteric coat surrounding the seating coat.

27. The pharmaceutical composition according to claim 26, wherein the core further comprises the glidant and the anti-adherent.

28. The pharmaceutical composition according to claim 26 or 27, wherein the sealing coat is Opadryl-IR-7000 White.

29. The pharmaceutical composition according to claim 29, wherein the amount of Opadryl-IR-7000 White is between 1 and 10% w/w.

30. The pharmaceutical composition according to claim 28 or 29, wherein the amount of Opadryl-IR-7000 White is about 3.1% w/w.

31. The pharmaceutical composition according to any one of claims 26 to 30, wherein the enteric coat is Sureteric YAE-6-18107 White.

32. The pharmaceutical composition according to claim 31, wherein the amount of Sureteric YAE-6-18107 White is between 1 and 20% w/w.

33. The pharmaceutical composition according to claim 31 or 32, wherein the amount of Sureteric YAE-6-18107 White is about 10.2% w/w.

34. The pharmaceutical composition according to any one of claims 26 to 33 , wherein the composition has a dissolution profile of greater than 80% at 45 minutes according to the United States Pharmacopoeia dissolution test in a 0.05M phosphate buffered solution having a pH of 6.8.

35. The pharmaceutical composition according to any one of claims 26 to 33 , wherein the composition has a dissolution profile of greater than 90% at 45 minutes according to the United States Pharmacopoeia dissolution test in a 0.05M phosphate buffered solution having a pH of 6.8.

36. The pharmaceutical composition according to any one of claims 26 to 33 , wherein the composition has a dissolution profile of less than 10% at 120 minutes according to the United States Pharmacopoeia dissolution test in 0.1N HCl.

37. The pharmaceutical composition according to any one of claims 26 to 33 , wherein the composition has a dissolution profile of less than 1% at 120 minutes according to the United States Pharmacopoeia dissolution test in 0.1N HCl.

38. The pharmaceutical composition according to any one of claims 1 to 37, wherein *in vivo* oral intake of between 15 and 60 mg/kg of the composition produces of maximum plasma level (Cmax) of pyridoxal 5'-phosphate of between 1 and 8 mg/l.

39. The pharmaceutical composition according to any one of claims 1 to 37, wherein *in vivo* oral intake of between 15 and 60 mg/kg of the composition produces an average plasma level of between 0.1 and 2 mg/l of pyridoxal 5'phosphate in the period from 2 hours after intake to 24 hours after intake.

40. A pre-blend for the manufacture of a pyridoxal-5'-phosphate oral dosage form comprising: pyridoxal-5'-phosphate or a pharmaceutically acceptable salt thereof and microcrystalline cellulose, wherein the pre-blend contains an amount of pyridoxal-5'-phosphate is greater than or equal to 80% by weight.

41. The pre-blend according to claim 40, wherein the pre-blend contains an amount of microcrystalline cellulose is greater than or equal to 10% by weight.

42. The pre-blend according to claim 40 or 41, wherein the amount of pyridoxal-5'-phosphate is about 84.8% w/w and the amount of microcrystalline cellulose is about 15.2% w/w.

43. The pre-blend according to claim 42, wherein the microcrystalline cellulose has a particle size of about 0.100 mm.

44. The pre-blend according to claim 42 or 43, wherein the microcrystalline cellulose is Avicel PH 102.

45. The pre-blend according to any one of claims 40 to 44, wherein the oral dosage form is a tablet.

46. The pre-blend according to any one of claims 40 to 44, wherein the oral dosage form is a capsule.

47. A method of preparing the pharmaceutical composition according to claim 1, comprising the steps of:

(1) granulating the pyridoxal 5'-phosphate or the pharmaceutical salt thereof, with the disintegrant, the binding agent, and the lubricant to provide a tableting preparation; and

(2) compressing the tableting preparation into a core.

48. The method according to claim 47, wherein step(1) further comprises blending the disintegrant, the binding agent, and the lubricant with a glidant and an anti-adherent.

49. The method according to claim 48, wherein the disintegrant is croscarmellose sodium; the binding agent is povidone and microcrystalline cellulose; the lubricant is magnesium stearate, the glidant is colloidal silicon dioxide, the anti-adherent is talc.

50. The method according to claim 49, wherein the microcrystalline cellulose have a particle size of about 0.100 mm.

51. The method according to claim 49 or 50, wherein the microcrystalline cellulose is Avicel PH 102.

52. The method according to claim any one of claims 59 to 51, wherein the povidone has a K value of between 27-33.

53. The method according to claim 52, wherein the povidone is PVP K30.

54. A method of according to claim 48, wherein step (1) comprises the steps of:

(a) dissolving 1 to 10 % w/w of the povidone in purified water to provide a granulating solution;

(b) mixing 50 to 80% w/w of the pyridoxal-5'-phosphate or pharmaceutically acceptable salt with 2 to 15% w/w of a first amount of microcrystalline cellulose to provide a pre-blend;

(c) mixing the pre-blend with the granulating solution to provide a first preparation;

(d) substantially drying the first preparation;

(e) mixing 2 to 15% of a second amount of the microcrystalline cellulose, 3.0% w/w of the croscarmellose sodium, 1 to 5% w/w of the talc and 0.1 to 3 % w/w of colloidal silicon dioxide to provide a second preparation; and

(f) mixing the first and second preparation with 1 to 2% w/w of magnesium stearate to provide the tableting preparation.

55. The method according to claim 48, wherein the amount of povidone is about 4.7% w/w; the amount of pyridoxal 5'-phosphate is about 66.3% w/w; the first amount of the microcrystalline cellulose is about 11.9% w/w; the amount of croscarmellose sodium is about 3.0% w/w; the second amount of the microcrystalline cellulose is about 10.3% w/w; the amount of the croscarmellose sodium is about 3.0%; the amount of magnesium stearate is about 1.1% w/w; the amount of talc is about 2.3% w/w; and the amount of colloidal silicon dioxide is about 0.6% w/w.

56. The method according to claim 54 or 55, wherein the pyridoxal-5'-phosphate and the first amount of the microcrystalline cellulose are mixed with a ribbon blender.

57. The method according to any one of claims 54 to 56, further comprising the step of passing the first preparation through a 12 mesh screen following step (c).

58. The method according to any one of claims 54 to 57, further comprising step of passing the first preparation through a 12 mesh screen following step (d).

59. The method according to any one of claims 54 to 58, further comprising the step of passing the second preparation through a 16 mesh screen following step (e).

60. The method according to any one of claims 54 to 59, wherein the first preparation is dried at 45°C using a forced air drying oven.

61. The method according to any one of claims 54 to 60, wherein the first and second preparations are mixed with a diffusive blender.

62. The method according to any one of claims 54 to 61, wherein the method further comprises the steps of:

(3) applying a sealing coat to the core to provide a sealed core; and

(4) applying an enteric coat to the sealed core.

63. The method according to claim 62, wherein the sealing coat is Opadryl-IR-7000 White.

64. The method according to claim 63, wherein the Opadryl-IR-7000 White is applied as a 15% w/w dispersion.

65. The method according to any one of claims 62 to 64, wherein the enteric coat is Sureteric YAE-6-18107 White.

66. The method according to claim 65, wherein the Sureteric YAE-6-18107 White is applied as a 15% w/w dispersion.

67. A method of reducing the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof, said method comprising the step of administering an effective amount of the pharmaceutical composition according to any one of claims 26 to 39.

68. Use of the pharmaceutical composition according to any one of claims 26 to 39, for reduction of the incidence of nausea and vomiting associated with the oral administration of pyridoxal 5'-phosphate or a pharmaceutically acceptable salt thereof.

Figure 1

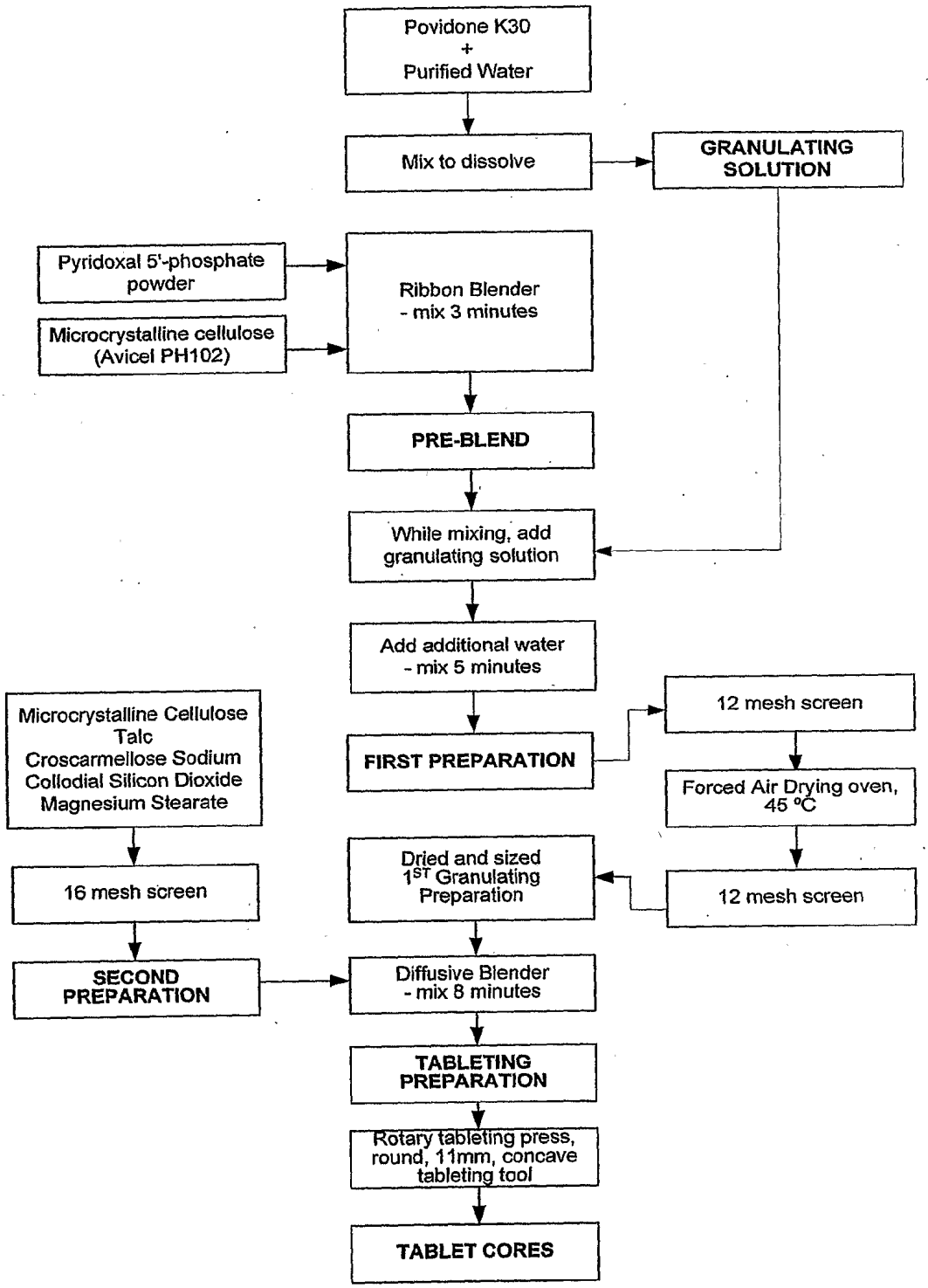
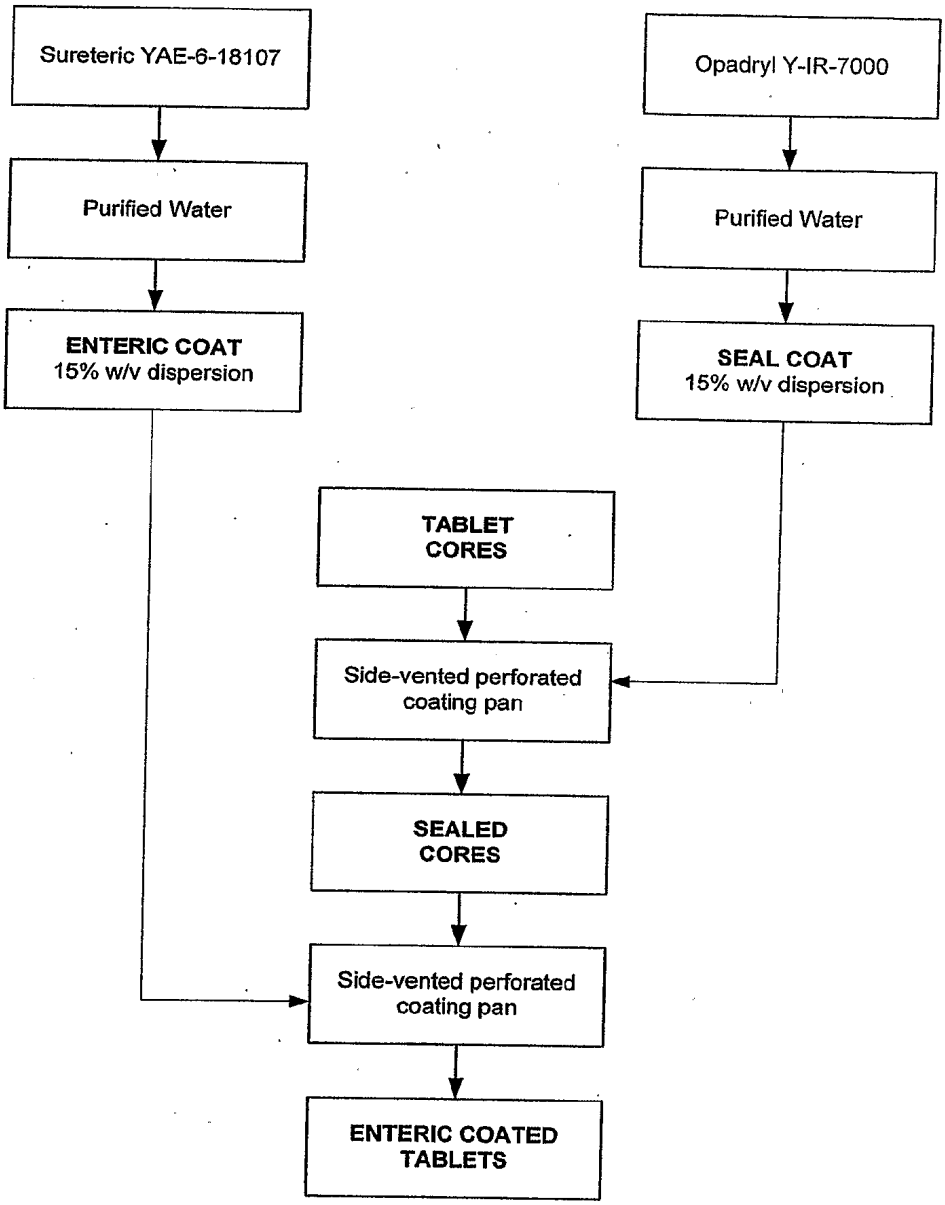

Povidone K30
+
Purified Water
Mix to dissolve
GRANULATING SOLUTION
Pyridoxal 5'-phosphate powder
Microcrystalline cellulose (Avicel PH102)
Ribbon Blender
- mix 3 minutes
PRE-BLEND
While mixing, add granulating solution
Add additional water
- mix 5 minutes
Microcrystalline Cellulose
Talc
Croscarmellose Sodium
Collodial Silicon Dioxide
Magnesium Stearate
FIRST PREPARATION
12 mesh screen
Forced Air Drying oven, 45 °C
Dried and sized 1ST Granulating Preparation
12 mesh screen
16 mesh screen
SECOND PREPARATION
Diffusive Blender
- mix 8 minutes
TABLETING PREPARATION
Rotary tableting press, round, 11mm, concave tableting tool
TABLET CORES

Figure 2


Sureteric YAE-6-18107
Purified Water
ENTERIC COAT
15% w/v dispersion
Opadryl Y-IR-7000
Purified Water
SEAL COAT
15% w/v dispersion
TABLET CORES
Side-vented perforated coating pan
SEALED CORES
Side-vented perforated coating pan
ENTERIC COATED TABLETS

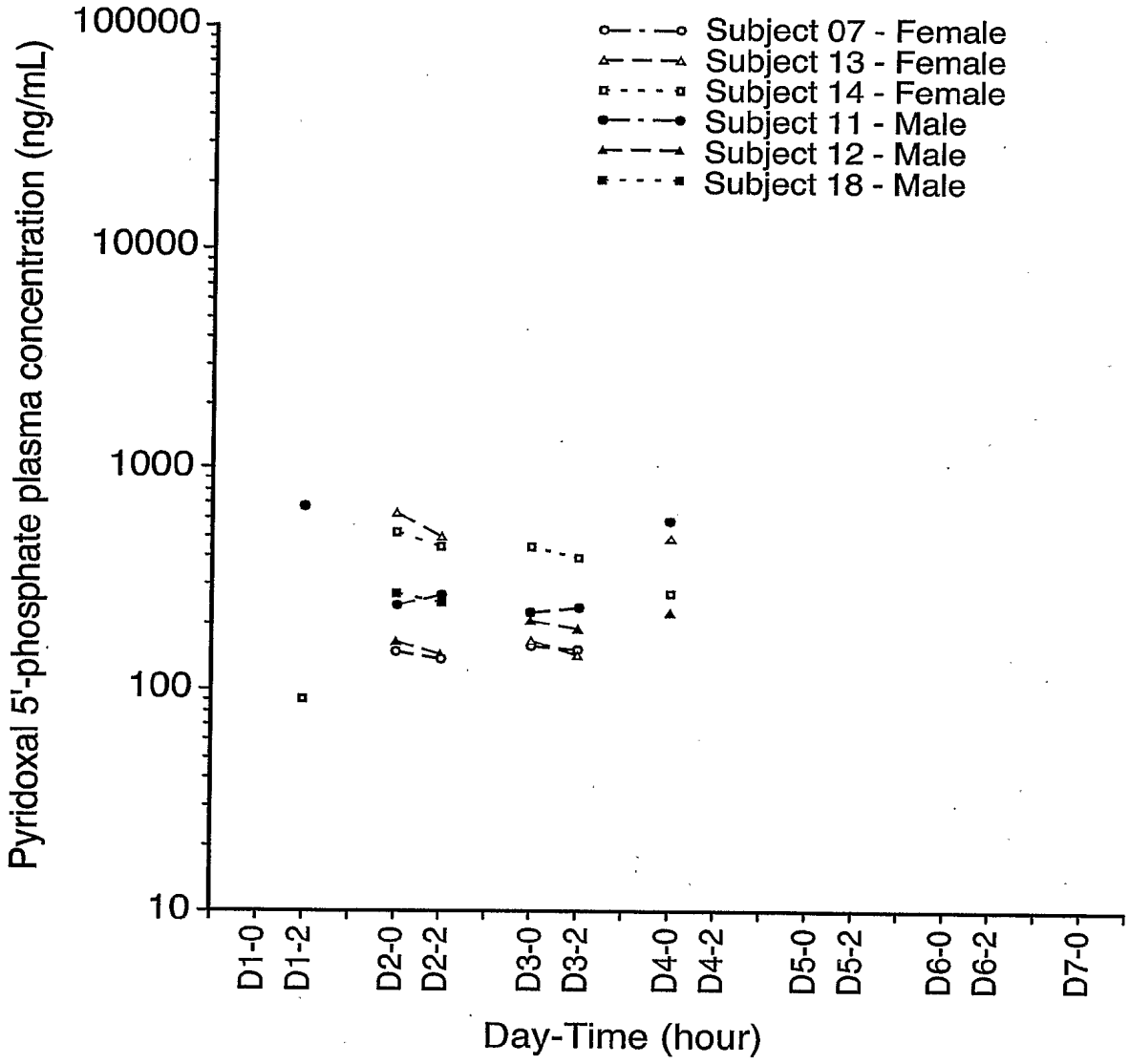

Subject 07 - Female
Subject 13 - Female
Subject 14 - Female
Subject 11 - Male
Subject 12 - Male
Subject 18 - Male
Pyridoxal 5'-phosphate plasma concentration (ng/mL)
100000
10000
1000
100
10
D1-0
D1-2
D2-0
D2-2
D3-0
D3-2
D4-0
D4-2
D5-0
D5-2
D6-0
D6-2
D7-0
Day-Time (hour)

FIG.3

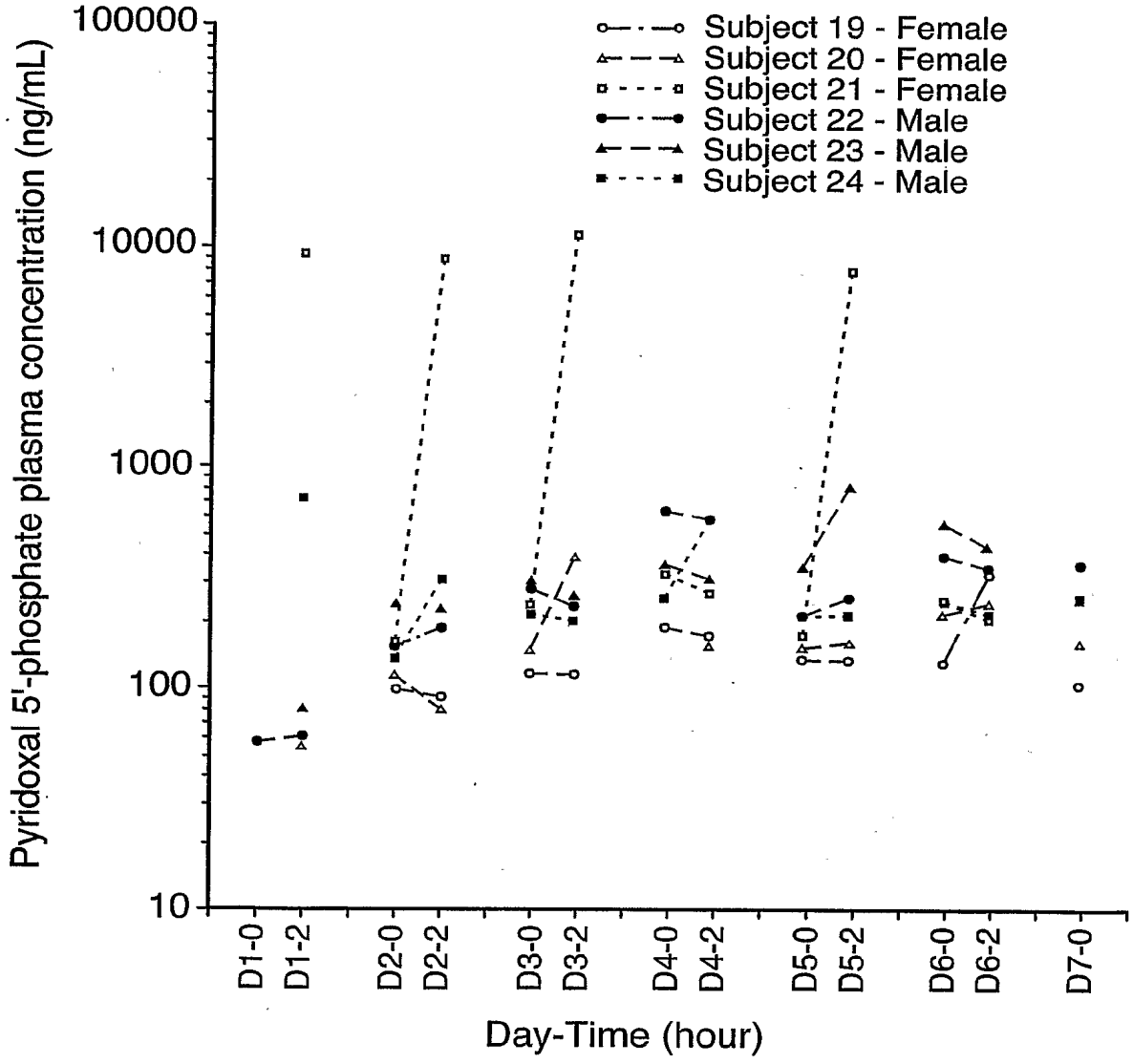

Subject 19 - Female
Subject 20 - Female
Subject 21 - Female
Subject 22 - Male
Subject 23 - Male
Subject 24 - Male
Pyridoxal 5'-phosphate plasma concentration (ng/mL)
100000
10000
1000
100
10
D1-0
D1-2
D2-0
D2-2
D3-0
D3-2
D4-0
D4-2
D5-0
D5-2
D6-0
D6-2
D7-0
Day-Time (hour)

FIG.4

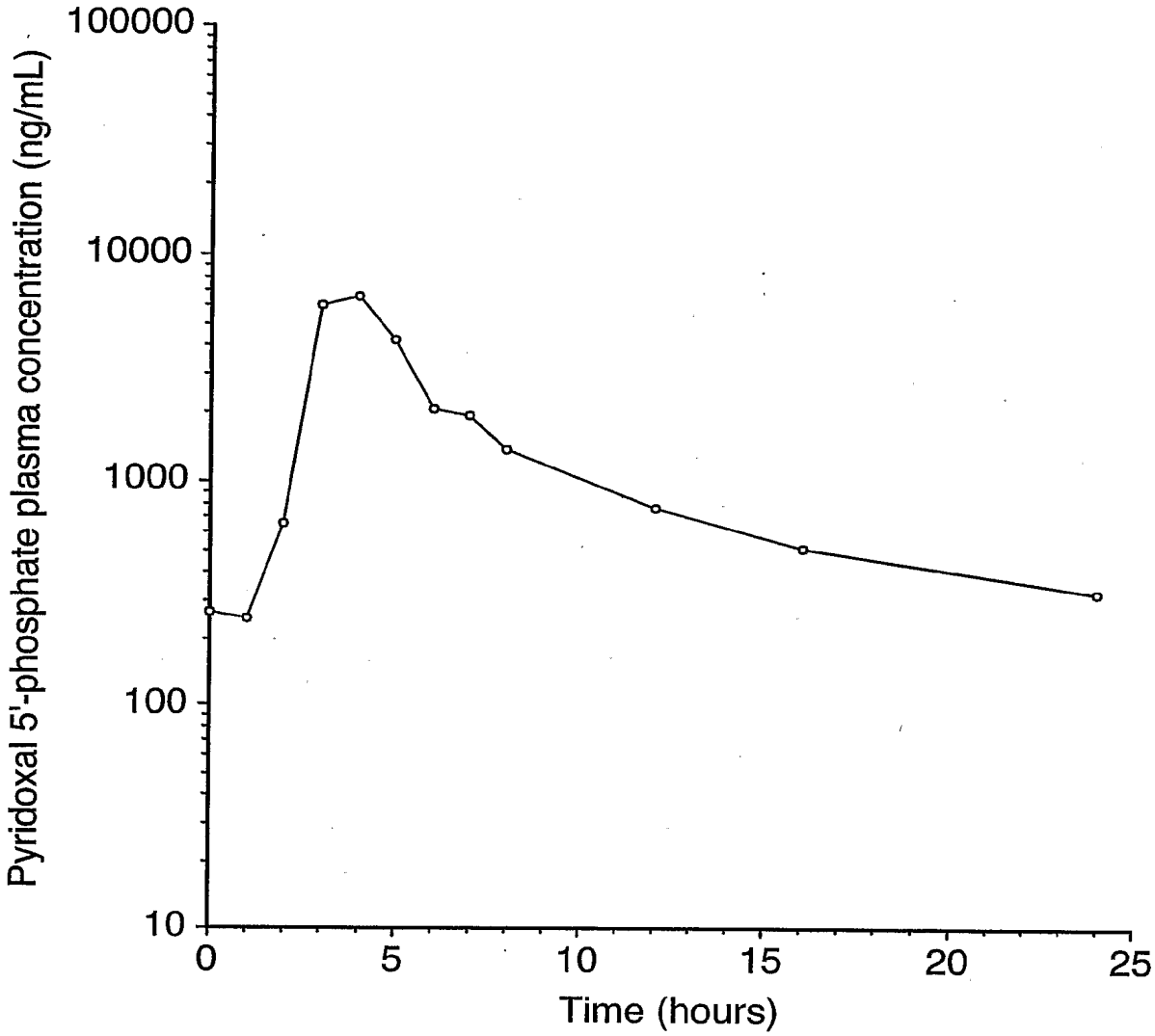

Pyridoxal 5'-phosphate plasma concentration (ng/mL)
100000
10000
1000
100
10
0
5
10
15
20
25
Time (hours)

FIG.5

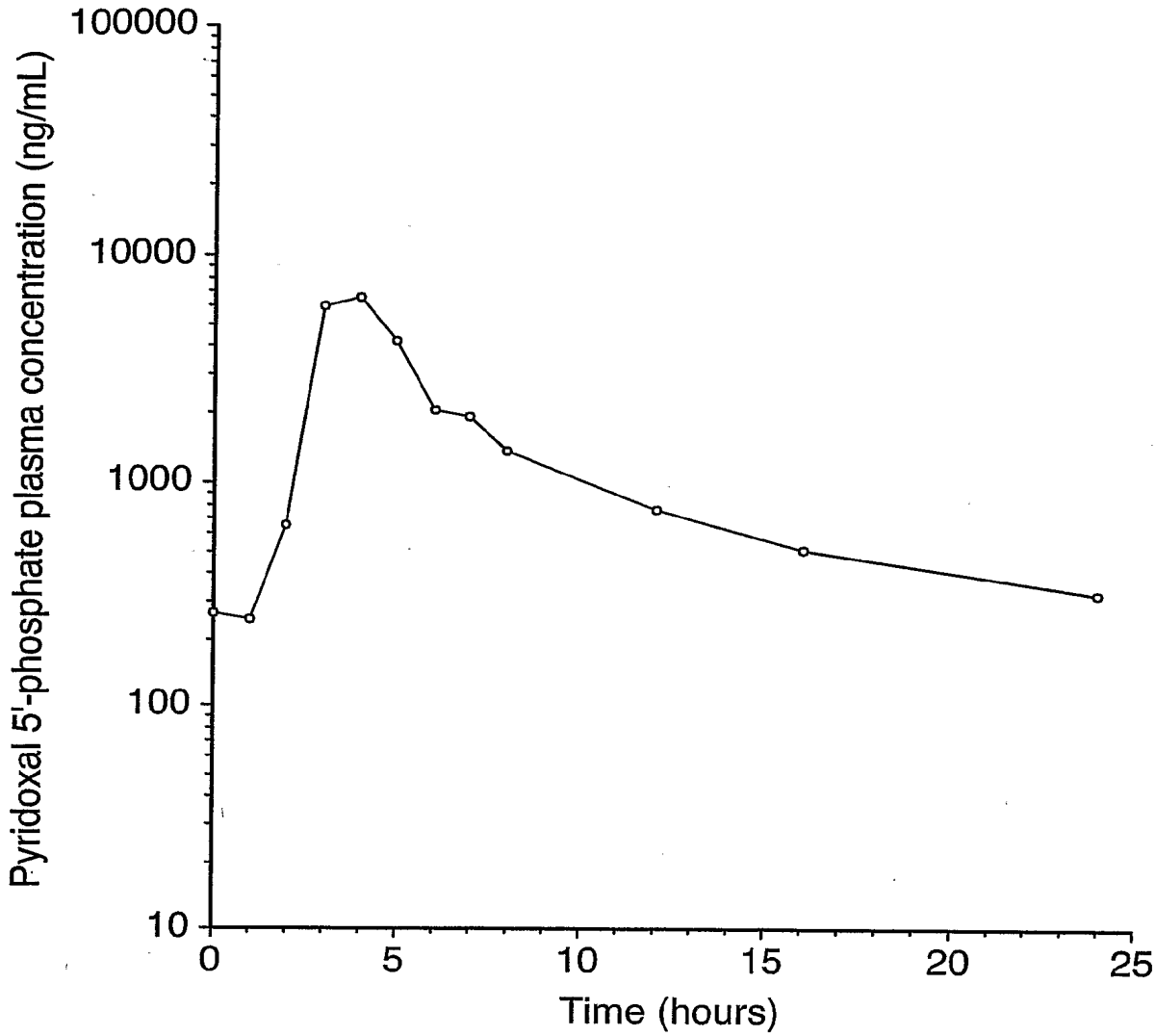

100000
10000
1000
100
10
Pyridoxal 5'-phosphate plasma concentration (ng/mL)
0
5
10
15
20
25
Time (hours)

FIG.6

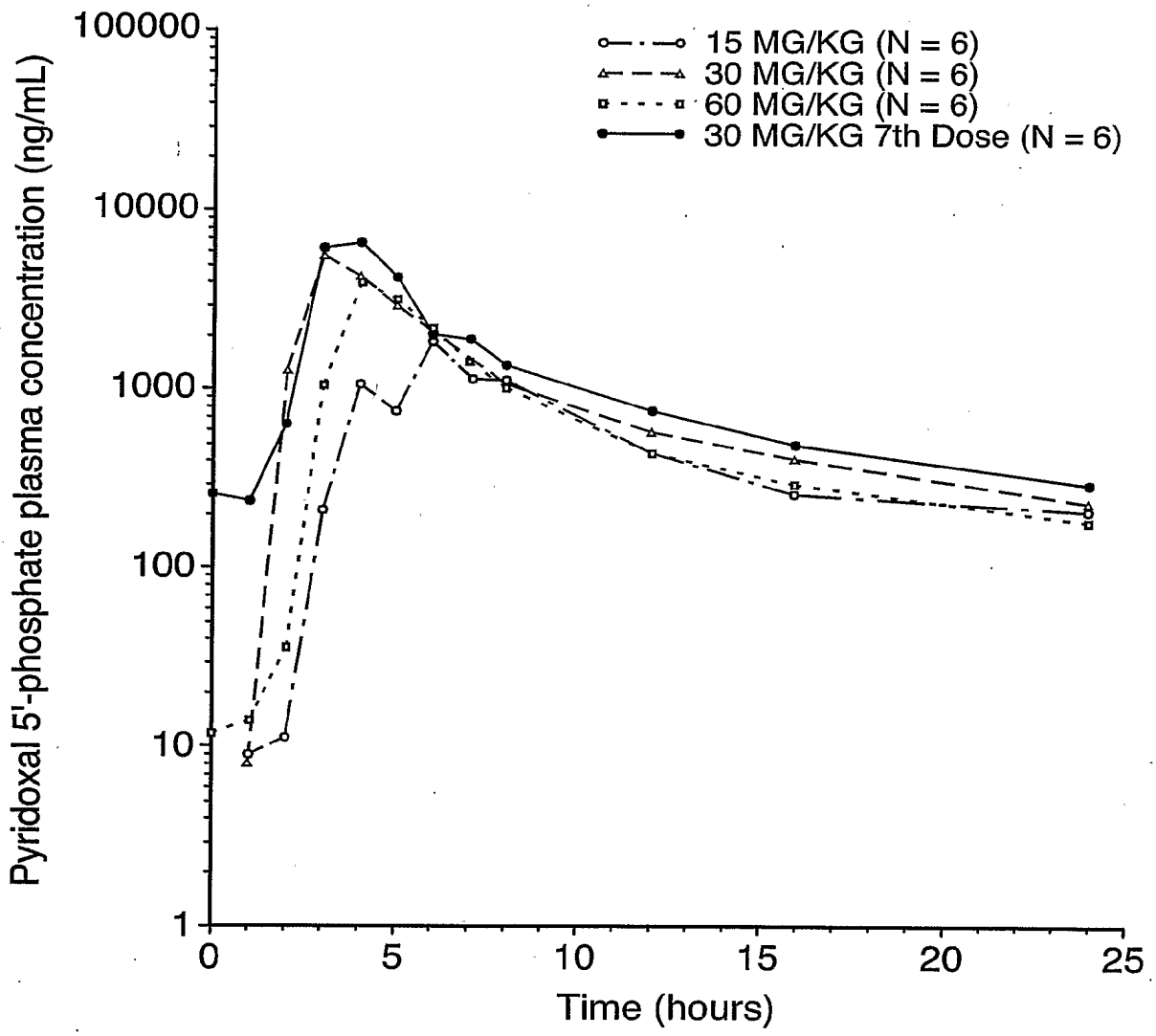

100000
10000
1000
100
10
1
Pyridoxal 5'-phosphate plasma concentration (ng/mL)
0
5
10
15
20
25
Time (hours)
15 MG/KG (N = 6)
30 MG/KG (N = 6)
60 MG/KG (N = 6)
30 MG/KG 7th Dose (N = 6)

FIG.7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001810

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/675*** (2006.01) , ***A61K 47/38*** (2006.01) , ***A61K 47/30*** (2006.01) , ***A61K 9/28*** (2006.01) , ***A61K 47/12*** (2006.01) , ***A61K 47/02*** (2006.01) , ***A61K 9/48*** (2006.01)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61K 31/675 (2006.01) , A61K 47/38 (2006.01) , A61K 47/30 (2006.01) , A61K 9/28 (2006.01) , A61K 47/12 (2006.01) , A61K 47/02 (2006.01) , A61K 9/48 (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
A61K*

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Delphion, espace@net, PubMed, Internet, Canadian Patent Data Base.
Keywords: Pyridoxal, pyridoxal-5'-phosphate, enteric, dissolution, bioavailable, tablet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUGITO, K. et al., Gastric Empting Rate of Drug Preparations. III. Effects of Size of Enteric Micro-Capsules with Mean Diameters Ranging from 0.1 to 1.1 mm in Man., Chem. Pharm. Bull., Dec. 1992, 40(12), pages 3343-3345. See page 3343 abstract, table I and first paragraph of Results section.	1-68

[ ] Further documents are listed in the continuation of Box C.

[ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 March 2006 (01-03-2006)	6 March 2006 (06-03-2006)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer James Martyn (819) 953-0761

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001810

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 67
because they relate to subject matter not required to be searched by this Authority, namely :

Claim 67, directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. Regardless, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claim 67.

2. [ ] Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.